dated: September 15, 1999

MEMORANDUM

SUBJECT: Response to Public Comments on the Preliminary Risk Assessments for the Organophosphate Tribufos

FROM: Anne Overstreet, Chemical Review Manager
Special Review and Reregistration Division
Office of Pesticide Programs

TO: OPP Public Docket for tribufos
Docket # **34148**

Introduction

This document addresses public comments that were received in response to EPA's Notice of Availability (63 FR 48213, September 9, 1998) of preliminary risk assessments for the seven Organophosphate chemicals: cadusafos, dimethoate, ethoprop, fenthion, sulfotepp, temephos and tribufos. Part I of this document addresses comments specific to tribufos (also known as tribuphos or DEF), and Part II focuses on non-chemical-specific comments. By "non-chemical-specific" we mean that the comment was submitted to the OPP Public Dockets for each of the seven chemicals or for a significant sub-set of the seven. Also, these non-chemical-specific comments generally apply to regulatory or science policy issues that are not unique to any one of the risk assessments. The comments are presented in **bold** and the response is in normal typeset.

Part I: Tribufos Specific Comments and Responses

A. Response to Comments on the HED Chapter

Comment: **Bayer commented that the residue levels used in the dietary risk assessment were exaggerated because they were based on data generated in a cotton metabolism study (MRID 42350009) performed in a greenhouse at an application rate three times higher than permitted by the DEF label. The purpose of the high application rate in the cotton metabolism study was to facilitate the identification of residues, not to quantitate residues. No correction was performed in the Agency's calculations to account for the exaggerated**

application rate. Consequently, the residues levels from this study which were used in the Agency's dietary risk assessment were too high.

Response: A refined Tier III chronic dietary analysis for tribufos was done using revised cottonseed, milk and meat anticipated residues. The results of the chronic analysis indicate that the chronic dietary risk estimates associated with the existing proposed uses of tribufos are below the Agency's level of risk concern (<100% of the Population Adjusted Dose).

Comment: Bayer identified two mathematical errors in the Agency's calculations:

> **1) The calculated anticipated residues in cotton raw agricultural commodities were based on a cotton metabolism study application rate which is three times higher than the rate permitted on the DEF label. Bayer states that they are opposed to the use of these values to calculate the dietary exposure, however; if these values are to be used, the Agency should have corrected these values for the dose exaggeration. Rather than using a residue value of 200 ppm for cotton gin byproducts, the Agency should have divided the measured residue of 175 ppm by three or at least have indicated that the residue levels and resulting dietary exposure are too large by some unknown amount.**
>
> **2) The dose exaggeration used in the cotton metabolism study should have been reflected in the calculation of the 1X dietary burden for the cattle feeding study (MRID 43821601). Based on the metabolism data, the 1X cattle dietary burden would be 15 ppm, and 120 ppm, corresponding to 0.6X, 2.2X, and 8X, respectively, which were appropriate feeding levels.**

Response: Subsequent to the issuance of the June 3, 1998 Preliminary Tribufos Risk Assessment, a field trial study for tribufos on the magnitude of the residue on cottonseed and cotton gin trash was received and reviewed by the Agency (MRID #444391-01). In the study the maximum field residue value for cottonseed was 2.8 ppm and 36.4 ppm for cotton gin byproducts. Based on these values from the study, HED recommends tolerances of 4.0 ppm (cottonseed) and 40.0 ppm (cotton gin trash).

On February 18, 1999, the Agency revised chronic anticipated residues for tribufos to use the aforementioned field trial data and percent crop treated data. Reduction factors derived from a processing study (MRID #43837801) were used for various cottonseed commodities. Determination of the dietary burden for ruminants was thus refined for exposure to tribufos residues on cotton gin byproducts used as animal feed. The chronic anticipated residues from cotton gin byproducts were recalculated to be 7.4 ppm (21 ppm average field trial value x 35% crop treated). The dietary burden for cattle is now calculated to be 1.6 ppm. These changes are reflected in the March 12, 1999 revised risk assessment. Acute and chronic dietary exposure and risk estimates for the U.S. population and all population subgroups for exposure to tribufos do not exceed the Agency's level of concern.

Comment: **Bayer noted EPA's evaluation contained a number of errors in the transcription and/or use of the data, including the calculation of exposures on a ug/lb ai basis, the calculation of transfer coefficients on a 50 gm/hr basis, and the best fit dislodgeable residue values on a ug/50 gm basis.**

Response: Specific errors were not provided in the rebuttal. Data from the mixer/loader/ applicator study (MRID 426859-01) were combined, as per EPA policy, with other surrogate data from the Pesticide Handlers Exposure Database (PHED) to increase the sample size and number of studies. The unit exposures reported in the risk assessment are not identical to those calculated by Bayer in their own study. However, the differences in the exposure assessments is not attributed to "errors" in the use of the data. The Agency combines chemical-specific data with available surrogate data to increase the sample size is in effect because individual chemical-specific studies do not necessarily encompass the variety of equipment in use throughout the country and the large variability of exposures among handlers. While data from PHED provides the best available information on handler exposures, it should be noted that some aspects of the studies included (e.g., duration, acres treated, pounds of active ingredient handled) may not accurately represent labeled uses in all cases. Therefore, the Agency would consider a more refined PHED estimate restricting some of the replicates selected in the subset (see Table 10 in the HED Risk Assessment - "Exposure Scenario Descriptions for the Use of Tribuphos") based on greater knowledge about the actual label uses and product packaging. Any refinements in the PHED subsets must also include an acceptable rationale for omitting data points.

The results of the handler exposures as reported in the occupational risk assessment (i.e., using the PHED data in combination with the chemical-specific study) do not significantly differ from the MOEs calculated using the data in the chemical-specific study. For illustrative purposes, the results of 2 of the 5 activities monitored in MRID 426859-01 are included in this rebuttal as a separate assessment for comparison with the risk assessment. MRID 426859-01 monitored aerial and groundboom applicators, open and closed mixing/loading, and flaggers. Assessments are provided below for the ***aerial and groundboom applicators*** using a short- and intermediate-term LOAEL of 2 mg/kg/day based on a 21-day dermal study (inhibition of plasma, RBC, and brain ChE activity). The uncertainty factor of 1,000 is applied (i.e., 10x for inter-species and 10x for intra-species extrapolation; and 10x due to the observance of severe neurotoxic effects seen in the hen study, indicating tribufos is a potent neurotoxicant and for the use of a LOAEL).

Aerial Applicators:

Summary (MRID 426859-01) - 8 replicates; dermal and inhalation PHED grade A (i.e., meets QA/QC requirements); applied to cotton; aerial enclosed cockpit; application rate ranged from 1.127 to 1.879 lb ai/acre; 605 to 1,061 acres treated per replicate; total amount handled ranged from 681 to 1,568 lb ai per replicate; and sampling time ranged from 4.22 to 5.05 hours. The Agency's risk assessment is based on a range of 656 to 2,250 lb ai handled to represent treatments of 350 to 1,200 acres at the maximum labeled rate of 1.875 lb ai/acre.

Exposure (MRID 426859-01) - The results of the dermal passive dosimetry data from MRID 426859-01 indicate a geometric mean exposure of 3.2 mg/day for the 8 replicates monitored in the study. This potential exposure represents the test subjects wearing long pants, long sleeved shirts, and no gloves while applying tribufos in an enclosed cockpit. The unit dermal exposure (geometric mean), normalized by the amount of ai handled, for these same 8 replicates is 0.0041 mg/lb ai. Table 1 illustrates that the exposure data from MRID 426859-01, as monitored in the field as well as extrapolated to a full day of application, does not significantly differ from that provided in the preliminary risk assessment . All three assessments clearly show that the MOEs are far below 1,000.

Table 1. Comparison of Aerial Applicator MOEs Using MRID 426859-01 and the Preliminary Risk Assessment.

Data Source	Potential Dermal Exposure(see units below) Long pants, long sleeved shirt, no gloves	Potential Dose (mg/kg/day)	MOE
MRID 426859-01; dermal data presented as monitored in the field	3.2 mg/day (range of 4.22 to 5.05 hours per replicate)	0.046	43
MRID 426859-01; dermal data are the unit exposures (0.0041 mg/lb ai) normalized by a full day's activity (i.e., 350 to 1,200 acres per day)	2.7 mg/day (0.0041 mg/lb ai x 1.875 lb ai/A x 350 acres)	0.039	51
	9.2 mg/day (0.0041 mg/lb ai x 1.875 lb ai/A x 1,200 acres)	0.13	15
Agency's risk assessment (see document for specific details)	3.3 mg/day (0.005 mg/lb ai x 1.875 lb ai/A x 350 acres)	0.047	43
	11 mg/day (0.005 mg/lb ai x 1.875 lb ai/A x 1,200 acres)	0.16	13

Groundboom Applicators:

Summary (MRID 426859-01) - 8 replicates; dermal and inhalation PHED grade A (i.e., meets QA/QC requirements); applied to cotton; groundboom tractor enclosed cab; application rate of 1.879 lb ai/acre; 51 to 80 acres treated per replicate; total amount handled ranged from 96 to 150 lb ai per replicate; and sampling time ranged from 3.95 to 4.77 hours. The Agency's assessment in the preliminary risk assessment is based on 150 lb ai handled to represent treatment of 80 acres at the maximum labeled rate of 1.875 lb ai/acre.

Exposure (MRID 426859-01) - The results of the dermal passive dosimetry data from MRID 426859-01 indicate a geometric mean exposure of 0.35 mg/day for the 8 replicates monitored in the study. This potential exposure represents the test subjects wearing long pants, long sleeved shirts, and no gloves while applying tribufos in an enclosed tractor cab. The unit dermal exposure (geometric mean), normalized by the amount of ai handled, for these same 8 replicates is 0.0039 mg/lb ai. Table 2 illustrates that the exposure data from MRID 426859-01, as

monitored in the field as well as extrapolated to a full day of application, does not significantly differ from that provided in the preliminary risk assessment. All three assessments clearly show that the MOEs are below 1,000.

Table 2. Comparison of Groundboom Applicator MOEs Using MRID 426859-01 and the Risk Assessment.

Data Source	Potential Exposure (see units below) Long pants, long sleeved shirt, no gloves	Potential Dose (mg/kg/day)	MOE
MRID 426859-01; dermal data presented as monitored in the field	0.35 mg/day (range of 3.95 to 4.77 hours per replicate)	0.0050	400
MRID 426859-01; dermal data are the unit exposures (0.0039 mg/lb ai) normalized by a full day's activity (i.e., 80 acres per day)	0.59 mg/day (0.0039 mg/lb ai x 1.875 lb ai/A x 80 acres)	0.0084	240
Agency's draft RED (see RED for specific details)	0.75 mg/day (0.005 mg/lb ai x 1.875 lb ai/A x 80 acres)	0.011	180

- **Errors in the transcription and/or use of the data in calculating the transfer coefficients (Tc) on a 50 gm/hr basis.**

Response: Specific errors were not provided in the rebuttal. In the preliminary risk assessment, the average transfer coefficient for 15, 17, and 20 DAT was calculated as the ratio of dermal exposure to the predicted residue data (dermal exposure in μg/hr divided by the predicted cotton boll residues (μg/50 gm samples)). The cotton boll residue data used in determining the transfer coefficients were based on the predicted values developed using a regression of the means of the triplicate samples. An argument could be made that the transfer coefficient should be based on the actual residue values monitored concurrently with the dermal samples. Table 3 presents the individual and average transfer coefficients based on predicted and actual residue data. The predicted values were used in the preliminary risk assessment because it was believed that the dissipation curve was more reliable than a triplicate sample monitored concurrently with the dermal dosimetry data. Table 4 presents the REIs calculated using both methods since the Agency has yet to develop a policy on the use of the actual versus the predicted residue data. Regardless of which method is selected, the REIs are within 1 to 7 days of each other and all are of a long duration (i.e., greater than 19 days).

Table 3. Transfer Coefficients (Tc) Based on Predicted and Actual Cotton Boll Residues.

Study Site	Interval (DAT)	Tc (50 g bolls/hour) based on **Predicted** Residue Data			
		Pickers	Module	Rakers	Trampers
CA - Aerial	15	44	41	67	No Data

CA - Aerial	17	118	No Data	357	213
CA - Ground	20	114	11	29	No Data
Arithmetic Means:		92	26	151	213
Study Site	DAT	Tc (50 g bolls/hour) based on **Actual** Residue Data			
CA - Aerial	15	36	33	55	No Data
CA - Aerial	17	23	No Data	68	41
CA - Ground	20	77	7	19	No Data
Arithmetic Means:		45	20	47	41

Rounding errors may have been introduced.
Tc (50g bolls/hr) = (dermal exposure (μg/hr) / cotton boll residue (μg/50g sample))
Cotton boll samples were collected at the CA aerial site on 0, 1, 2, 4, 7 through 13, 15, and 17 DAT; and at the CA ground site on 0, 1, 2, 4, 7 through 13, 15, 16, 17, 18, and 20 DAT.

Table 4. Comparison of the REIs Using Tc from the Predicted Residues (Risk Assessment) and the Actual Residues.

Job Function	DAT[a]	Draft RED[b]		Comparison REIs	
		Tc (50g bolls/hr) based on Predicted Residues	REI (days)	Tc (50g bolls/hr) based on Actual Residues[c]	REI (days)[d]
Pickers (n=10)	15, 17, and 20	92	26	45	23
Module (n=6)	15 and 17	26	20	20	19
Rakers (n=10)	15, 17, and 20	151	28	47	23
Trampers (n=4)	20	213	30	41	23

a DAT = Days after treatment that the dermal samples were collected.
b Results as reported in the preliminary risk assessment using predicted residues to calculate the Tc.
c Tc based on the actual residues monitored concurrently with the dermal dosimetry samples.
d REI (days) is set on the day that the MOE $\geq$ 1,000. Where Dermal MOE = 2 mg/kg/day LOAEL/ Dermal Dose (mg/kg/day). Where Dermal Dose (mg/kg/day) = (Residues (μg/50g sample) * Tc (50g/hr) * 0.001 mg/μg conversion * 8 hr work day) / 70 kg.

The transfer coefficients developed using the data in MRID 427016-01 represent harvesting activities of "pickers, module builders, rakers, and trampers". The cotton harvesting methods that use these particular activities and other potential methods that may be completely mechanical were not described fully in the study. Mechanical harvesting, without the need for these specific activities, may be an acceptable risk mitigation option to reduce the REIs. More information on cotton harvesting methods from Bayer would aid in determining risk mitigation measures.

- **Errors in the transcription and/or use of the data in calculating the best fit dislodgeable residue values on a μg/50 gm basis.**

Response: Specific errors were not provided in the rebuttal. The predicted daily residue values in the preliminary risk assessment are based on a regression of the means of the triplicate samples at each site, and then the predicted residues for each day, at all four sites, averaged together. The Agency acknowledges that the regression for each of the four sites might be better expressed using the individual triplicate samples in determining the predicted dissipation for that site. Furthermore, REIs could be calculated for each of the four sites and the longest REI could be selected instead of the average as reported in the preliminary risk assessment.

The interpretation on how to use the cotton boll residue data in determining the transfer coefficient is discussed in the above mentioned response. In brief, the transfer coefficients were calculated using the predicted residue values in the preliminary risk assessment. Another option would be to use the actual residue values monitored concurrently with the dermal passive dosimetry. The comparison of the transfer coefficients and resulting REIs are in Table 4 above.

Comment: Bayer states that the occupational portion of the risk assessment incorrectly assumes that the exposure data are normally distributed and uses the arithmetic mean as a measure of central tendency rather than a geometric mean which provides a more representative measure of central tendency for log-normally distributed data.

Response: Bayer is correct that the use of an arithmetic mean assumes a normally distributed data set and that most exposure data are log-normally distributed. However, the handler unit exposure data in the risk assessment did not assume that the data were normally distributed. In fact, PHED categorizes the distribution of exposure values for each body part (e.g., chest, upper arm) as normal, log normal, or "other" (i.e., neither normal nor lognormal). A central tendency value is then selected from the distribution of the exposure values for each body part. These values are the arithmetic mean for normal distributions, the geometric mean for log-normal distributions, and the median for all "other" distributions. Once selected, the central tendency values for each body part are composited into a "best fit" exposure value representing the entire body. In most instances, the unit exposure values are representative of median to geometric mean values.

The post application risk assessment is based on arithmetic mean dermal exposures in

determining the transfer coefficient, and thereby, assumed a normal distribution. The arithmetic means were used because each activity (e.g., pickers) for each DAT is represented by only 3 or 4 samples.

Comment: The Agency incorrectly stated that Bayer evaluated the blood cholinesterase activity of the mixer/loader/applicators and harvesters because it was required by CDPR. Instead the plasma and erythrocyte cholinesterase activity of all workers in these studies was measured during the entire tribufos use season as an inherent part of Bayer's overall evaluation strategy. Accordingly, the results clearly indicate there were no exposure-related effects associated with tribufos under actual use conditions.

Response: The risk assessment stated in regard to the study above (MRID 426859-01) that *"although cholinesterase was also evaluated as a biological endpoint, this was not a biomonitoring study per se. Note that cholinesterase was monitored as required by the study protocol and California Environmental Protection Agency's Department of Pesticide Regulations (CDPR) guidelines. CDPR requires that workers be removed from pesticide handling in the event of significant cholinesterase depression."* To clarify the intention of this statement, the biological monitoring of cholinesterase does not determine a dose level (mg/kg/day) that can be used in the quantitative MOE assessment.

Nonetheless, in MRID 426859-01 the group mean percentages of post-exposure baseline values for all job activities ranged from 95.8 - 106.9 percent of baseline erythrocyte cholinesterase levels and 95.9 - 107.5 percent of baseline plasma cholinesterase levels. The lowest mean post-exposure value, as a percentage of baseline for erythrocyte cholinesterase, for an individual worker over a four week interval (i.e., test subject "I" for ground crew mixer/loaders using closed mixing equipment) was 92.2±5.3. The lowest level, as a percentage of baseline, during this four week interval was 87.4. The lowest level was monitored at the two week interval. The baseline was established using 3 pre-exposure samples. Based on California's Title 3 (April 1998), none of the test subjects' plasma cholinesterase levels fell below a level of concern[1]. However, the Agency's regulatory endpoint for tribufos is plasma, erythrocyte, and brain cholinesterase inhibition and the Agency uses uncertainty factors beyond a no effect level.

[1] Title 3 states: *"The employer shall remove an employee from exposure to Organophosphate or carbamate pesticides if the employee's plasma cholinesterase level falls to 60 percent or less of baseline, or if red cell cholinesterase falls to 70 percent or less of baseline. The employee shall be removed from further exposure until cholinesterase values return to 80 percent or more of their respective baseline values.*

An additional concern was noted during the review of the rebuttal. The Agency calculates

a total exposure/risk when the endpoint for two exposure routes are the same. However, even though the endpoints are based on the same effect, the risk assessment reported the dermal and inhalation MOEs separately. This oversight has been corrected and this comment response presents the total risk using the endpoint for the dermal route (see above for value) and the short- and intermediate-term inhalation endpoint from a 90-day inhalation study. The inhalation NOAEL for plasma cholinesterase is 2.43 mg/m^3 (converted to a dose of 0.9 mg/kg/day) with an uncertainty factor of 100. Table 5 summarizes the combined risk using the dermal and inhalation MOEs from the data in Tables 8 and 9 of the Risk Assessment. Only the risks associated with the maximum risk mitigation measures (i.e., engineering controls) are reported. The inhalation MOEs for the engineering controls for the mixer/loaders, groundboom applicators, and flaggers are not in Table 9 of the preliminary risk assessment. These MOEs were calculated specifically for this memo because the inhalation MOEs were above 100 at lower risk mitigation measures (i.e., open systems).

The uncertainty factors for the dermal and inhalation routes are different (i.e., dermal = 1,000 and inhalation = 100). Therefore, the Agency has developed a method for combining routes of exposure with different uncertainty factors. This method is know as an Aggregate Risk Index (ARI) in which the uncertainty factors are normalized to 1 and the targeted level of uncertainty is an ARI > 1.

Table 5 (on the following page) summarizes the mixer/loader/applicator scenarios and subsequent risk to handlers.

Table 5. Handler Aggregate Risk Index.

Exposure Scenario[a]	MOEs[b]		Aggregate Risk Index (> 1 targeted)[c]
	Dermal	Inhalation	
Mixer/Loader Risk Estimate			
Mixing/loading Liquids for Aerial Applications (1a)	Typical 25	1,200	0.025
	Max. 7	330	0.0070
Mixing/loading Liquids for Groundboom Applications (1b)	110	5,000	0.11
Applicator Risk Estimate			
Aerial Fixed-Wing Applications (2)	Typical 43	1,400	0.043
	Max. 13	410	0.013
Helicopter Applications (3)	HED no longer assess helicopter separately from aerial		
Groundboom Sprayers (4)	180	9,800	0.18
Flagger Risk Estimate			
Flagging (5)	Typical 950	2,700	0.92
	Max. 280	820	0.27

Typical = 350 acres and Max. = 1,200 acres treated.

[a] Long pants, long sleeved shirts, no gloves (except for mixer/loaders using chemical resistant gloves) while using closed mixing systems and enclosed cabs/trucks.

[b] Dermal MOEs listed in Table 8 of the RED. Inhalation MOEs listed in Table 9 of the RED (unit exposure for M/L = 0.083 μg/lb ai, groundboom applicator = 0.043 μg/lb ai, and flagger = 0.035 μg/lb ai). High confidence data for all new values, a 90 percent protection factor assumed for a flagger in a closed truck.

[c] ARI = 1/((1/(dermal MOE/1000 UF)) + (1/(inhalation MOE/100 UF))), UF = uncertainty factor.

Comment: Bayer disagrees with the Agency's determination that the LOAEL from a 21-day dermal toxicity study is the appropriate or best toxicological endpoint for short-term and intermediate-term risk assessments. Bayer states that the dermal absorption study on DEF 6 should be used with NOELs from repeated-dose toxicity studies to evaluate the hazard from short and intermediate-term exposures.

Response: Listed below, are the reasons that the Agency selected the LOAEL from the 21-day dermal toxicity study to assess dermal risk from exposure to tribufos.

1. In the toxicology database of a pesticide, the guideline study that is most applicable to dermal risk assessment is the 21-day or the 90-day dermal toxicity study in rats or rabbits. The

dermal toxicity studies are preferred because: 1) the experimental conditions (dermal applications, 6 hrs/day for 5 days/wk) simulate human dermal exposure to pesticide handlers (mixers, loader and applicators), and 2): the treatment regimen (6 hrs/day, 5 days/wk for either 21 or 90 days) encompasses the exposure period of concern for workers (i.e., short-term, 1-7 days or intermediate-term, 7 days to several months).

2. As stated by Bayer, the "... ideal study for route-related assessment is one performed by the same route by which field exposure occurs." - the 21-day dermal toxicity study does indeed fit this condition.

3. The critical toxic effect (cholinesterase inhibition) was demonstrated after exposure via the dermal route and duration of concern (21 days) in this study.

4. The results of the rabbit dermal study are supported by similar results observed in a 90-day dermal neurotoxicity study in hens. In this study, at the lowest dose tested (2.6 mg/kg/day), blood cholinesterase inhibition was demonstrated. In addition, neuropathology was seen at the highest dose (42 mg/kg/day) and accordingly a NOAEL was not established.

5. If an oral study were used along with a 44% dermal absorption rate, the resulting equivalent oral dose would be comparable to the 2.0 mg/kg/day that is currently being used for the risk assessment. For example: the oral NOAEL of 1.0 mg/kg/day (from the acute neurotoxicity study) with a 44% dermal absorption rate would yield a dermal equivalent dose of 2.2 mg/kg/day ($1.0 \div 0.44 = 2.27$ mg/kg/day), so there would be no significant difference in the dose used for the risk assessments.

6. Although the registrant objects to the use of the 21-day dermal study because it was conducted using the technical formulation, they recommend the use of an oral study which was also conducted with the technical formulation.

7. In response to the registrant's contention that the 21-day dermal study tested the technical product while the workers are exposed to the formulated end-use product; the Agency would evaluate the merits of using the results of a dermal toxicity study with the formulated end-use product for dermal risk assessment if the registrant chooses to conduct such a study.

8. Additionally, in March, 1997, the Agency's FIFRA Advisory panel, approved the use of the dermal studies for dermal risk assessment during their evaluation of the Toxicology Endpoint Selection (TES) process.

B. Response to Comments on the EFED Chapter

Comment: Bayer commented on the Agency's findings concerning the adequacy of the field dissipation study of tribufos on Georgia soil (MRID 43325501; Bayer report No. 105163).

Response: The Agency has reviewed the above mentioned study and has determined that it cannot be used to fulfill the guideline requirement for several reasons including the fact that only 29% of the applied tribufos was accounted for immediately after treatment. Also, it was not clear to the Agency what the route of dissipation was in this study. The 26-day half-life was not supported by the laboratory studies which indicate that tribufos is very stable to both chemical and microbial degradation. Other possible routes of dissipation, including accumulation in plants, volatilization, and leaching are also not supported by the laboratory data. While it is not unusual to observe faster degradation in the field compared with the laboratory, the differences seen here were not justified.

Comment: Bayer commented on the Agency's findings concerning the field dissipation of tribufos on California soil (MRID 42350005; Bayer report No. 100156) and the Agency's determination that the study is unacceptable and does not fulfill the guideline requirement.

Response: This study is unacceptable and cannot be used towards the fulfillment of the terrestrial field dissipation guideline requirement since the data were too variable to accurately assess the dissipation of tribufos. Immediately after treatment, the concentration of tribufos in 15 samples collected from the 0- to 6-inch soil depth varied by >10X.

It is also not clear what the route of dissipation was in this study. The rapid decline in residues during the first week cannot be explained, given the information in the laboratory studies. The laboratory studies show that tribufos is very stable to both chemical and microbial degradation. Other possible routes of dissipation, including accumulation in plants, volatilization, and leaching are also not supported by the laboratory data.

Comment: Bayer states that the EPA erroneously identified a risk of chronic and reproductive effects to birds. Bayer maintains that avian species are not exposed to significant tribufos residues on a chronic basis. Also, it is very unlikely that treated vegetation would be used as avian food items in the fall after cotton harvest, and would be impossible for this to occur during the following spring when avian breeding occurs. Bayer further states that typically after the field transition is completed, a new crop is planted sometime during December through March. They claim this replanting further decreases the likelihood of contaminated avian food items being available during the spring.

Response: The Agency is concerned that both migrating and endemic avian species will be present in cotton fields during the fall application, as well as over the winter. While it is not known if a single exposure can cause adverse reproductive effects, the fact that tribufos is very persistent and immobile in soil suggests that significant residues will remain regardless of degradation of the cotton plant itself. In addition, food crops (e.g. corn, fall vegetables, soybeans, and peanuts), planted in the fields after cotton defoliation may be an even better attractant to wildlife.

Maximum residues (a single application of 1.875 lbs of active ingredient per acre) range from 28.125 to 450 ppm for the Kenega food group items. It is clear that residues may exceed

the avian NOEL (148 ppm for quail; eggshell thinning at the LOEC of 262 ppm) very easily even if only half of the maximum residue (450 ppm/2 = 225 ppm) is used.

Part II: Non-Chemical-Specific Comments and Responses

Non-chemical-specific comments were received from: Idaho Farm Bureau Federation (separate comments dated 11/6/98 and 1/18/99); National Cotton Council; Natural Resources Defense Council (NRDC); American Farm Bureau Federation; Fish and Wildlife Service, Division of Environmental Contaminants; Southern Professional Fruit Workers Conference (held at Clemson University); and 14 individuals, 13 of whom identified themselves as pest control operators (PCOs) or otherwise associated with the professional pest control industry.

Because there are several recurring issues in the comments that were submitted, we have chosen to divide our responses into two sub-sections. In order to avoid repetition, sub-section A deals with comments that are closely related and were repeated in more than one of the submissions, and with comments that are testimonial in nature. Sub-section B responds to those comments that are unique to each submission and refers the reader to the appropriate common responses in sub-section A.

A. EPA Responses to Recurring Issues in the Non-Chemical-Specific Comments

1. Comments Related to Common Mechanism of Toxicity

Comments: Several commentors, including the NRDC and Private Citizen Abbotts, questioned why EPA has not considered a common mechanism of toxicity in these OP risk assessments.

Response: EPA is required under FQPA to consider available information on the effects of cumulative exposure to the pesticide and other substances with common mechanisms of toxicity. EPA believes that the Organophosphate pesticides should be considered to operate via a common mechanism of toxicity, cholinesterase inhibition, unless and until the Agency receives data demonstrating otherwise.

In the Federal Register of August 6, 1998 (63 FR 42031), EPA issued a notice announcing the availability of the proposed EPA pesticide policy guidance document entitled "Guidance for Identifying Pesticide Chemicals That Have a Common Mechanism of Toxicity for Use in Assessing the Cumulative Toxic Effects of Pesticides." The guidance document describes the approach that EPA proposes to use for identifying and categorizing pesticide chemicals that have a common mechanism of toxicity for purposes of assessing the cumulative toxic effects of such pesticides. The 60-day comment period ended October 8, 1998. The revised guidance was issued in February, 1999. In developing this document, the Agency solicited advice from the FIFRA Scientific Advisory Panel (SAP) in February 1997; a year later (March 1998), OPP reported its progress to the SAP.

With respect to the comments that EPA has not considered common mechanism in these assessments, the Agency acknowledges that it has not yet performed a cumulative risk assessment, because the methodology for conducting such assessments is still being developed. Since there are currently no standard methods for doing cumulative risk assessment, EPA is pursuing an open, peer-reviewed process to develop approaches to cumulative risk assessment. The Agency is also nearing completion of the revision of the Chemical Mixtures Risk Assessment Guidelines, which present methods for combining risks from multiple chemicals. In addition, the International Life Sciences Institute (ILSI) is independently exploring appropriate methods and developing a framework for performing a cumulative risk assessment. ILSI held a workshop on this subject in September 1998, and recently submitted a report to the Agency outlining its findings. The Agency will continue its ongoing efforts in this area along with examining the ILSI work and other sources of information in preparation for release of an Agency draft guidance document. This guidance document is currently scheduled for late summer/early fall of 1999 with a 60-day comment period.

2. Comments Related to Additional Data and Default Assumptions

Comments: The American Farm Bureau Federation, The National Cotton Council and Private Citizen Abbotts encouraged EPA to obtain the data necessary to conduct realistic risk assessments. A common theme was that EPA should use actual data, particularly usage data, and avoid default assumptions in its assessments. Private Citizen Abbotts encouraged EPA to cancel all registrations, rather than make assumptions, when required data are missing. He particularly cited data gaps in the sulfotepp database.

Response: In phase four of reregistration, EPA exercised its data call-in authority to require studies to upgrade chemical databases to current scientific standards. Most of the OPs were subject to reregistration DCIs and registrants have been allowed ample time to submit those studies. EPA makes its reregistration and tolerance reassessment decisions on the best data that are available. Where data are incomplete, EPA may compensate by using an additional uncertainty factor or making a reasonable health-protective assumption. This has long been EPA practice, and is reinforced by FQPA's emphasis on the importance of the use of an additional safety factor where data are incomplete.

It should be noted, however, that the OP risk assessments in the docket are "preliminary," and that many of the first assessments were completed prior to receipt of all data. During the public comment and response period, EPA has continued its evaluations of available data, e.g., Monte Carlo analyses, for these seven chemicals, and these evaluations have been incorporated into the refined risk assessments. In general, if additional, pertinent data are submitted prior to or during the comment periods, EPA will take these data into account in its revised assessments.

In response to private Citizen Abbott's comments on sulfotepp, EPA recognizes that the databases for certain chemicals are inadequate. In those instances, EPA will use scientific assumptions which are protective of the public health to conduct its risk assessment until adequate

data are developed. The Agency will assume that the risks using these scientific assumptions are accurate and will proceed, if necessary, to identify and implement the appropriate mitigation strategies.

For a discussion of the sources of use and usage data and how EPA employs these data in its assessments, the reader is referred to a science policy paper entitled, "The Role of Use-Related Information in Pesticide Risk Assessment and Risk Management," which will be available shortly for public comment.

3. Comments Related to Application of the FQPA 10X Safety Factor

Comments: The NRDC commented that EPA failed to demonstrate the existence of reliable data for most OPs to justify departure from the use of the FQPA 10X safety factor. They also requested that EPA offer an explanation as to why the additional safety factor not be retained for all OPs that are not supported by a developmental neurotoxicity study.

Response: OPP has developed criteria for retaining, reducing, and removing the additional ten-fold safety factor provided for in the FQPA to account for special susceptibility of infants and children to the effects of pesticide exposures. These criteria involve a weight-of-evidence consideration of both the nature and severity of effects observed in young animals, as well as the adequacy of the data base for the chemical. OPP's rationale for these criteria has been reviewed at various stages of development by the Scientific Advisory Panel (SAP). OPP has completed a draft Standard Operating Procedure (SOP) that provides procedural guidance at the working level for making recommendations for retaining or modifying the 10-fold factor. The SOP was presented to the Scientific Advisory Panel in December, 1998.

In addition, an Intra-Agency workgroup is looking at general considerations regarding the FQPA safety factor decisions such as: establishing procedures for consistency and documentation; ensuring the adequacy of the data set for decision-making; and establishing criteria for retaining or modifying the FQPA factor.

The Agency's policy for applying the FQPA 10-fold safety factor is currently one of the science policy issues being prepared for public comment. Both the SOP and the Intra-Agency workgroup draft guidance document will be completed and issued for comment. These issues will be discussed further at the upcoming SAP meeting in May, 1999.

The question of what constitutes a reliable data base for making decisions related to the FQPA safety factor, including whether or not a developmental neurotoxicity study is required, is being thoroughly reviewed. Once that review process is completed, EPA may need to revisit its SOPs and decide how best to incorporate the revised procedures into its ongoing decision making process.

4. Comments Related to Highly Exposed Populations

Comments: NRDC noted that EPA failed to consider the increased potential for pesticide exposure to "sentinel" populations, such as farm worker children.

Response: NRDC has petitioned the Agency to designate farm children as a major identifiable subgroup under the FQPA. The Agency is currently evaluating the scientific and legal issues raised in that petition. Specifically related to the preliminary risk assessment for the first OPs, EPA acknowledges that exposures to farm worker children were not evaluated separately, i.e., as a distinct population sub-group. However, based on the limited data currently available to characterize actual pesticide exposure to children of agricultural workers, such as a 1997 biomonitoring study by Loewenherz, Fenske and others (Environ. Health Perspect. 105:1344-1353), we believe that the exposure estimates developed by EPA using the Agency's Residential Exposure SOPs and other available information are reasonably inclusive of the exposures likely to be experienced by this sub-group.

EPA is concerned about the disproportionate exposure of farm children to pesticides and has several ongoing projects designed to both assess and reduce these exposures. Some of EPA's major efforts in this area are described below.

EPA's major external research program, Science to Achieve Results (STAR) program allocated funds in fiscal year 1996 for three years of research on the most urgent issues regarding exposure of children to pesticides. The studies are looking at major ways children can be exposed (touching, eating, crawling, etc.) and at seasonal and locational differences, including agricultural settings. This research will support regulations and public education efforts that are more fully protective of children, for example through revised use restrictions and labeling requirements, and improved training and public information materials. Under the STAR program, the University of Arizona is assessing exposure of the children of seasonal and migrant laborers to agricultural pesticides. In addition, the University of Washington is assessing on a comprehensive seasonal basis, children's exposures to Organophosphate pesticides.

EPA's National Center for Environmental Research and Quality Assurance of the Office of Research and Development is funding a grant with the University of California at Berkeley for a five-year study, that began in August 1998, to quantify the exposure of children in agricultural areas of California to pesticides. The project will integrate biological research with community-based intervention efforts. The study will determine the impacts of pesticide exposure on children's growth and development. The University will also work with the farm worker community to investigate approaches for reducing these exposures.

Finally, based on recommendations from the Children's Health Protection Advisory Committee (CHPAC), EPA has committed to conduct a national assessment of implementation and enforcement of the Worker Protection Standard, including its effectiveness in addressing the safety needs of women and children as agricultural workers.

5. Comments Related to Relying on Sound Science

Comments: The National Cotton Council, American Farm Bureau Federation and Private Citizen Abbotts all supported EPA's reliance on sound science to make regulatory decisions. The National Cotton Council encouraged the Agency to finalize the nine science policy issues identified during the Tolerance Reassessment Advisory Committee (TRAC) before making regulatory decisions.

Response: EPA is committed to the principles outlined by Vice President Gore to have an open and transparent process, a reasonable transition to alternative products, and the use of sound science. It is primarily for that reason that the TRAC was formed and the pilot process for increased public participation in pesticide decisions was developed. However, EPA must balance the goal of providing for greater transparency and participation in development of science policy with its mission to ensure the safety of the food supply and the health of consumers, especially children, workers, and the environment. In order to accomplish our mission through timely decision making, EPA has established an ambitious schedule for completion of individual OP risk assessments and development of risk mitigation options. It should also be noted that FQPA does establish a statutory deadline to complete the reassessment of existing tolerances by 2006, and the Agency is making every effort to comply with that deadline.

6. Comments Related to a Transparent Process

Comments: The National Cotton Council, the American Farm Bureau Federation, Natural Resources Defense Council (NRDC) and Private Citizen Abbotts applauded EPA's efforts to make a transparent process for the reregistration of the Organophosphate pesticides. NRDC felt that further efforts were needed to ensure that all risk assessment methods used to establish tolerances (e.g. Monte Carlo methods and underlying assumptions) were transparent. Private Citizen Abbotts noted that the formats for risk assessments were not always consistent, that the "bottom line" risk could not always be determined, and that a table summarizing risks for all OPs would help in making risk management decisions.

Response: EPA agrees that a transparent process is essential to maximizing the benefits of the Organophosphate pesticides while minimizing the risks. The Tolerance Reassessment Advisory Committee (TRAC) was established to ensure that the process for the reregistration of the Organophosphate pesticides was transparent and open to all. EPA intends to continue its dialogue with the various constituents throughout the reregistration process.

EPA acknowledges inconsistencies in the assessments for the first 16 OPs. In many cases, the assessments were begun many months ago and have not been constantly updated to reflect new formats. In the revised risk assessments, we have made an effort to ensure consistency in the assumptions and the levels of refinement that are applied, given the data for each chemical. In an attempt to make the risk assessments easier to understand and compare, EPA has prepared risk summary and overview documents for each OP. These risk overview documents have been

prepared in a standard, logical format and are intended to assist the reader by identifying key features and findings of the risk assessments, highlighting any assumptions and refinements that have been used, and discussing ways of further refining the risk assessments. EPA agrees that a table format may be an effective tool in comparing risks for various OPs.

7. Comments Related to Transitioning to Safer Alternatives

Comments: American Farm Bureau Federation expressed concern that EPA administer FQPA in a practical and realistic way by allowing sufficient transition time for users to adapt to new or alternative products and practices. In his letter, Private Citizen Abbotts advocated linking approval of safer chemicals with cancellation of corresponding "older, riskier alternatives."

Response: The Agency recognizes the diversity of views exhibited by these comments.

EPA agrees with Private Citizen Abbotts that safer chemicals are preferable to more risky alternatives and, thus, has established an expedited registration process to accommodate and encourage newer, safer pesticides. When cumulative risk is the issue, as with the Organophosphate pesticides, the existence of a proven safer alternative may help when risk mitigation measures are necessary. When a safer chemical is registered, it may take several years of use on actual field crops before its ability to completely replace another chemical is known and recognized.

B. EPA's Response to Submitter - Specific Comments

1. Comments from Private Citizens

Comment: Private Citizen John Abbotts submitted a detailed 15-page letter outlining his views on the Agency's Preliminary Risk Assessments and made several suggestions for improvements. In addition to the comments addressed above, Mr. Abbotts indicated that some of the risks presented in the preliminary assessments were substantive enough to trigger immediate regulatory action by the EPA.

Private Citizen Abbotts also advocated that the EPA quickly process all deletions of particular uses requested by registrants. He particularly cited a letter where the registrant for dimethoate, Cheminova, requested cancellation of all dimethoate residential uses. Similarly, Mr. Abbotts requested that the EPA revoke all tolerances for which there are no registered uses.

Private Citizen Abbotts expressed concern that the EPA was allowing other pesticides, such as cadusofos, to remain on the market, even though the risk assessment used residues of ½ the Limit of Detection (LOD) and percent crop treated data rather than tolerance

level residues and 100% crop treated. He felt that the risks were unacceptable using 100% crop treated and tolerance level residues. Mr. Abbotts also suggested that EPA establish import tolerances based on toxicological data so that consumption at tolerance level would result in acceptable dietary risk.

Private Citizen Abbotts also made several suggestions for implementing a risk-reduction strategy for the Agency to begin reducing the cumulative risks posed by organophosphates. These suggestions included requiring each registrant to reduce the cumulative risk from all of their Organophosphate registrations to acceptable levels, requiring registrants to work together to reduce the risk on each commodity to a level consistent with the commodity's proportion of the diet, or creating market-based incentives for reducing the risks to organophosphates.

In his letter, Mr. Abbotts also maintains that the Agency should examine cumulative occupational risk.

Response: EPA disagrees that the risks outlined in the assessment for these seven chemicals are significant enough to require immediate regulatory action. All of these assessments are preliminary in nature and thus the stated risks likely overestimate the actual risk posed by the use of the chemical. Before demanding risk mitigation measures that may adversely affect the safety of the U.S. food supply, EPA has a duty to ensure that the risk assessment is as refined, and thus realistic, as possible.

EPA also agrees with Mr. Abbotts assertion that use deletions should be processed quickly. However, registrants frequently propose to delete uses to mitigate risks without actually submitting amendments to remove those uses from their labels. In addition, other registrants may have registered products with the same uses and be unwilling to remove them from their labels. Unless all registrants of a particular chemical request to delete these uses from their labels, these uses will still remain as part of the risk assessment. Finally, the Agency is committed to analyzing the risks and benefits, where appropriate, of Organophosphate pesticides during the reregistration process. This includes vetting proposed deletions with the grower community and other members of the public before taking any regulatory action. The TRAC (Tolerance Reassessment Advisory Committee) has been specifically established to promote dialogue among the public, grower groups and industry on the reregistration of Organophosphate pesticides.

As Mr. Abbotts is aware, FQPA establishes a statutory deadline to complete the reassessment of existing tolerances by 2006. The Agency is making every effort to comply with that deadline. As part of this goal, EPA is in the process of taking actions to revoke all tolerances for which there are no registered uses and that are not needed for import purposes.

In a worst-case risk assessment, such as that referenced by Mr. Abbotts for cadusofos, EPA typically assumes tolerance level residues and 100% crop treated. These worst-case assessments are used for screening purposes only and are an attempt to conserve Agency resources. To further refine dietary exposure, EPA calculations may include percent-crop-treated data, averages

of field trial data or other information. The refined exposure estimates are so designated because they are more likely to approximate the pesticide residues we anticipate humans will actually consume in their diets.

Many samples do not have quantifiable/detectable residues. Often, a residue chemistry data set for a given crop/chemical/data source combination of potential use in exposure refinement contains some samples that are reported as not bearing detectable or quantifiable residues, i.e., residues are less than the LOD. This is frequently the case for early season applications, long treatment-to-harvest intervals, and/or monitoring of the food supply closer to the point of consumption. Given the above information, the Agency has chosen to assign a residue value of ½ LOD (or ½ LOQ if an LOD has not been determined) to samples with no detectable residues if it is known or believed that these samples have been treated with a pesticide. This is believed to represent a minimal distortion of reality if only a small proportion (e.g., less than approximately 10-15%) of the data are below detectable limits. The use of ½ LOD for nondetectable samples is widely used in the risk assessment community and is advocated by EPA when the appropriate conditions are met as in the cadusafos risk assessment. For further discussion, please see the draft science policy paper entitled, "Assigning Values to Nondetected/Nonquantified Pesticide Residues in Human Health Dietary Exposure Assessments," (dated 11/30/98).

EPA currently establishes import tolerances using a technique similar to that used to establish domestic tolerances. The translated labels used overseas and the foreign field trial data are evaluated. A number of field trials are required which must demonstrate a range of climate conditions and cultural practices. These variations can lead to a range of residue values, which can vary from non-detectable to large concentrations. Using data from the field trials, EPA performs its risk assessment, refining residues as necessary. If the risk is acceptable, EPA establishes a tolerance at a level that is higher than the highest residue value obtained in the field trial data as it does when establishing a tolerance for use of a pesticide domestically.

Mr. Abbotts is suggesting that import tolerances be set in a reverse-type of process in which the toxicity data is combined with the consumption data to indicate the highest allowable pesticide concentration in the commodity. Although Mr. Abbotts' proposal might result in a more efficient review process for the Agency, such an abbreviated process would provide no assurances to farmers applying pesticides to their crops at the labeled application rates that the resulting produce would contain residues below the established tolerance levels. EPA believes that tolerances should be set at levels that are protective of human health. EPA is also obligated to ensure that use at the labeled application rate will not result in produce containing residues that are greater than the tolerance level. Field trial data are needed to ensure that the produce grown will indeed contain residues at levels below the established tolerance.

The Agency appreciates Private Citizen Abbotts proposals for risk mitigation strategies and, in fact, has initiated preliminary discussions about particular risk mitigation strategies that may cut across pesticides or commodities. The Agency expects that these discussions will likely address the value of particular uses irrespective of the identity of the pesticide or registrant.

EPA recognizes that farm workers may be exposed to multiple chemicals, however, as Mr. Abbotts mentions, occupational risk is not included in the FQPA statutory requirements for cumulative assessments. Therefore, EPA does not have the resources available to conduct such assessments and must continue to assess occupational risk based on a single chemical. Once the Agency establishes a method for determining cumulative exposure, it may be able to expand its guidelines to include occupational exposure scenarios.

See also responses to A1, A2, A5, A6 and A7 above.

Comment: **Thirteen individuals, who identified themselves as pest control operators requested that EPA: base its decisions on actual pesticide use, obtain necessary information through data call-ins, establish and communicate uniform policies to guide consistent implementation of FQPA, refrain from taking regulatory action based on unrealistic default assumptions.**

Response: See responses to A2, A5 and A6 above.

2. Comments from Universities and Extension Services

Comment: The Southeastern Professional Fruit Workers Conference, the annual meeting of applied fruit scientists (held at Clemson University in October, 1998) provided their evaluation of the OPs (and other pesticides) that are crucial in resistance management and IPM programs for crops in their area.. The group identifies opportunities for mitigation (primarily reductions in numbers of applications and increased PHIs).

Response: This comment was submitted in response to the second group of seven OPs. However, because it pertains to some of the first nine and none of the second group of seven, it was addressed it in the earlier response document to the first nine OPs.

3. Comments from Growers, Commodity and Marketing Groups

Comment: The National Cotton Council is concerned that exposures from gin trash as a feed additive are grossly overestimated. No cotton uses should be canceled based solely on unacceptable risk resulting from gin byproducts using current EPA assumptions. (Note: OPs with cotton uses include azinphos-methyl, methyl parathion, phorate, profenofos, naled, dicrotophos, and tribufos) The Council is working with the Agency to "adjust" these assumptions and indicated that they will be submitting additional data, but did not propose a submission date.

Response: EPA representatives met October 13, 1998, with a delegation from National Cotton Council (NCC) in response to their request to discuss cotton gin byproducts (CGB) and its proportion in livestock feeds. In addition to members of the NCC, representatives of cotton

ginners associations (Texas Cotton Ginners Association, Southeastern Cotton Ginners Association, and the California Cotton Ginners Association) were present. These experts are familiar with CGB, its volume of production in the USA, and its use as animal feed.

EPA discussed how a risk assessment is performed, i.e., how CGB are factored into the beef and dairy cattle diets and how potential transfer of residues to meat and milk could therefore affect a person's daily dietary intake of pesticide residues. Table 1 of OPPTS Test Guidelines Series 860 currently lists CGB as a raw agricultural commodity comprising up to 20% of the diet of beef and dairy cattle.

Representatives of the ginners associations agreed that in some parts of the country CGB are fed at up to 10% of the diet to beef cattle when the cattle first enter the feed lot. CGB are then reduced to approximately 3% in the finishing rations. Based on this information, the NCC has asked EPA to reconsider how CGB are currently listed in Table 1.

EPA asked the NCC to provide detailed information concerning the disposition and use of CGB. Information submitted should be able to be independently verified by OPP. The NCC submitted a protocol for obtaining such information. EPA has approved the protocol and is currently awaiting submission of this information.

See also responses to A2, A5, and A6 above.

4. Comments from Environmental and Consumer Groups

Comment: The Natural Resources Defense Council (NRDC) submitted a copy of their report, "Trouble on the Farm," and provided comments on four broad issues: 1) EPA fails to demonstrate the existence of reliable data for most OPs to justify departure from the use of FQPA 10X safety factor; 2) Preliminary assessments do not provide reasonable certainty of no harm, e.g. EPA did not consider "sentinel" population of farm worker children; 3) EPA must conduct a cumulative assessment; and 4) Often, e.g. azinphos-methyl, occupational risks are unacceptable even with maximum mitigation. These should be eliminated expeditiously

In addition, the NRDC urged EPA to account for "enantiomer" and metabolite toxicity in reassessing tolerances for the OPs. Enantiomers are mirror image molecules produced in the manufacture of Organophosphate active ingredients. Specifically, the commentor raises concern over the possibility that specific enantiomers of these substances could be produced during manufacture, and that these enantiomers may be more toxic than other enantiomers that may be present. Hence, the risks posed by these substances could be greater than the risks anticipated by EPA.

Response: EPA intends to complete risk assessments for individual OPs, taking into account any comments received during the public comment period. For the seven OPs, the public comment

period closed on the risk assessments in November, 1998. According to the plan developed by the TRAC, EPA will respond to comments on the risk assessments and work with USDA and stakeholders to develop risk management options for risks of concern, including workers. The risk management options will be subject to another 60-day comment period.

The comment response document for the first nine OPs also responded to a comment from a private citizen on the enantiomer toxicity. Enantiomers of a given substance are isomers whose mirror images are not superimposable. Enantiomers have identical physicochemical properties, except in the direction in which they rotate a plane of polarized light. The Agency agrees with NRDC's comment that enantiomers of a given substance may vary in toxicity and, therewith, pose different risks to human health or the environment. In a given manufacturing process it is possible that more than one specific enantiomer can form, unless the reaction conditions and feedstocks are such that formation of only one enantiomer is possible. It is also possible that one enantiomer may be produced more readily than an other enantiomer, and may predominate in the technical product. Even if an enantiomer is formed in low concentration relative to another enantiomer during synthesis of a technical product, it may still contribute significantly to the overall risk of the product if its toxicity is greater than the toxicity of the other enantiomer. Technical products of pesticide substances that can exist as two or more enantiomers usually do not undergo purification procedures that remove a specific enantiomer. These pesticide substances are generally used as obtained from synthesis, and are often comprised of more than one enantiomer. Individual enantiomers of a substance may interconvert in plants, mammals or the environment. Hence, a specific enantiomer of a substance may be converted into its other enantiomer as a result of plant or animal metabolism, or release into the environment. It is also possible for a substance that cannot exist in enantiomeric forms (i.e., is achiral) to be metabolized to other substances for which enantiomers are possible and are formed.

The Agency also agrees with NRDC's comment that metabolites (e.g., plant, farm animal, or mammalian metabolites) of a pesticide substance are often sufficiently toxic so as to contribute to the overall risks associated with use of the pesticide and consumption of foods that contain the pesticide and its residues. In some instances a metabolite may have substantially greater toxicity than its parent substance.

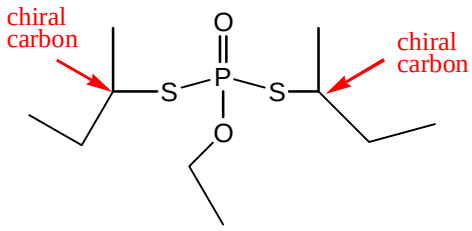
OPP believes, however, that its risk assessments of the seven subject organophosphorus pesticides adequately take into account the toxicity of any of their enantiomers or metabolites. In assessing the risks posed by a given pesticide substance, OPP evaluates a number of factors that may contribute to risk. These include, for example: the mammalian toxicity of the parent substance; its mammalian metabolism from different routes of exposure; its metabolism in plants and livestock (e.g., dairy cows, steer, poultry); the known or potential toxicity of mammalian, plant and livestock metabolites; the environmental fate and ecotoxicity of the parent substance; dietary exposure to the parent substance and its plant and livestock metabolites; exposure that may result from consumption of waters that contain the pesticide or environmental degradates thereof; and exposure that may result from residential or occupational use of the pesticide. Plant and livestock metabolites of toxicological concern are identified by OPP from an evaluation of plant and animal metabolism studies required for registration or reregistration.

OPP also routinely evaluates the manufacturing processes used to synthesize pesticide active ingredients as part of its process to evaluate the risks posed by pesticides. Submission of information pertaining to method of manufacture is required for registration and reregistration of pesticide substances. The primary purpose of evaluating a manufacturing process of a given pesticide is to ascertain the composition of the technical product with regard to overall risk to human health and the environment. The evaluation includes an analysis and consideration of: the feedstocks, reagents, catalysts, solvents and any other substances used in the process; reaction conditions; pesticide yield; byproducts, and any other substances that are known, or could reasonably be anticipated to form under the reaction conditions of the process. OPP considers any impurities in the reactants or other substances used in the synthesis that may contaminate the technical product and contribute to overall risk. Once a method of manufacture has been reviewed and deemed acceptable by OPP, the registrant must use that method of manufacture. The registrant cannot change or modify a method of manufacture until the Agency has evaluated the method and its impact on overall risk of the pesticide technical product. Thus, the composition of a pesticide technical product as manufactured from a process deemed acceptable by OPP should remain consistent among different lots.

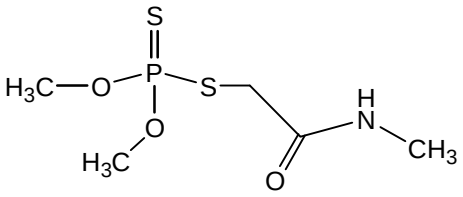
As stated above, technical products of pesticide substances that exist as two or more enantiomers often do not undergo purification procedures that remove a specific enantiomer, and these pesticide substances are generally used as obtained from synthesis. Current guidelines do not require that registrants provide OPP with information regarding which particular enantiomers are present, or their relative concentrations. OPP is generally unaware of which specific enantiomers or concentrations thereof are present in pesticide technical products. However, the presence and concentrations of specific enantiomers comprising a technical product are not expected to vary among manufactured lots because the same method of manufacture is used for each lot. While the Agency may not be aware of the presence or concentrations of specific enantiomers comprising the technical product of a pesticide substance for which enantiomers are possible, mammalian toxicity data required for registration (or reregistration) of the technical product represent the combined toxicity of the pesticide (including any enantiomers that are present) and its mammalian metabolites.

Environmental fate laboratory studies involving a pesticide substance are typically conducted using radiolabelled substance in which the substance is radiolabeled in at least at one site of the molecule. The Agency recognizes, however, that a specific enantiomer of a substance could convert to another enantiomer under actual environmental conditions. Environmental photolysis, for example, may lead to interconversion of one enantiomer to another. OPP evaluates geometrical, configurational and/or conformational isomer interconversions that occur in the environment, but only for those chemicals known to show specific isomer bioactivity. That is, one or more of the isomers are the only ones associated with pesticidal activity over the other isomers.

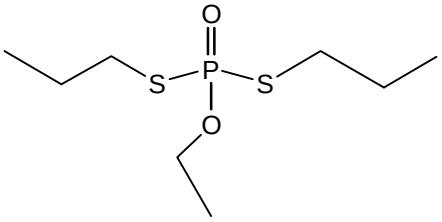
The structures of the seven subject organophosphorous substances are shown below:



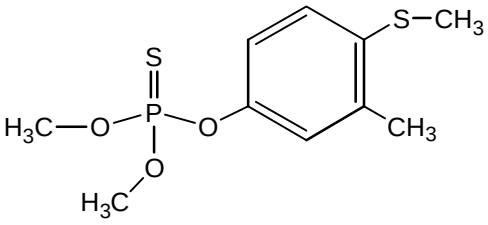
cadusafos



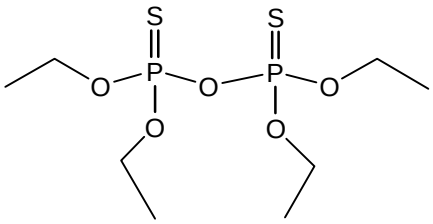
dimethoate



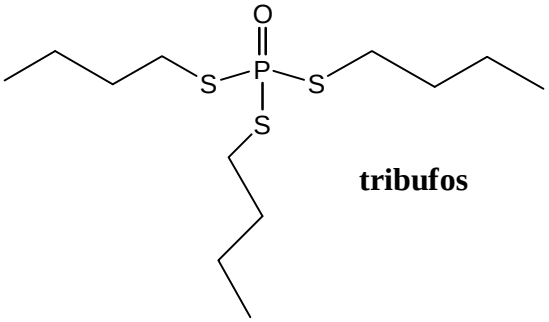
ethoprop



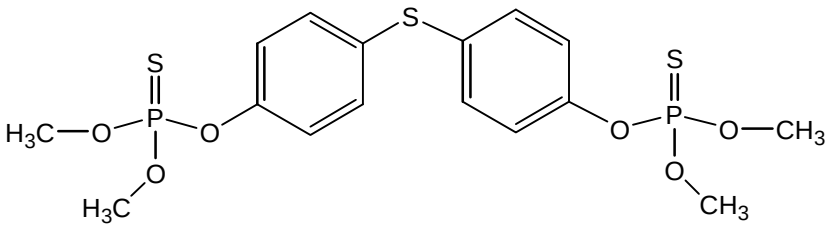
fenthion



sulfotep



tribufos



temephos

Of these seven substances only cadusafos can exist in enantiomeric forms. This substance has two chiral carbon atoms (as indicated) and, thus, a total of four distinct enantiomers are possible. The other six substances do not contain any atoms that are chiral and, therefore, it is not possible for them to exist as enantiomers. It is theoretically possible, however, that any of the seven substances could be metabolized in plants or mammals or degraded in the environment to other substances that could exist as enantiomers. Hydrolysis of one of the S-P bonds in ethoprop, for example, would result in a substance that has a chiral phosphorus atom and could exist as two distinct enantiomers.

The Agency does not know the relative ratios of the specific enantiomers in the technical product of cadusafos. However, the mammalian toxicity studies submitted by the registrant correspond to the technical product as manufactured and reflect the actual toxicity of the technical product and its metabolites. The same is also true for the cadusafos ecotoxicity studies submitted to the Agency. Therefore, even if one (or more) of the four enantiomers of cadusafos is (are) substantially more toxic than the other enantiomers, and is present in the technical product, its toxicity is expressed in the mammalian and ecotoxicity data submitted to the Agency and used in OPP's risk assessment of the technical product. The Agency does not expect differences in the composition of technical cadusafos among lots because the method of manufacture is (or will be) the same for each lot.

The environmental fate studies submitted for cadusafos were not intended to follow the fate of its individual enantiomers, or monitor for enantiomeric interconversions. Hence, OPP does not know to what extent, if at all, if the individual enantiomers of cadusafos interconvert in the environment. However, ecotoxicity data collected under current OPPTS test guidelines represent the ecotoxicity of the technical product (including any of its enantiomers that may be present), and its environmental degradates.

As previously stated, dimethoate, ethoprop, fenthion, sulfotep, tribufos, and temephos do not contain any chiral atoms. These substances cannot exist in isomeric forms that are enantiomeric. Thus, the possibility of specific enantiomers having greater toxicity than other enantiomers, or that one enantiomer may be interconverted to another in the environment do not apply to these substances. While it is possible that any of these substance can be metabolized to substances that contribute to the toxicity of the parent substance, the mammalian toxicity data submitted for each of these substances and used for risk assessment purposes represent the combined toxicity of the parent substance and metabolites thereof. Also, any plant or livestock metabolites of toxicological concern have been identified by OPP and included in the risk assessment of these substances.

See also responses to A1, A3, A4 and A5 above

D. EPA's Response to Comments from Other Federal Agencies

Comment: The Fish and Wildlife Service, Division of Environmental Contaminants,

pointed out that four of the seven OPs have Final Biological Opinions (1989) for Endangered Species. In addition, FWS and EPA are currently in consultation on fenthion. FWS recommends that EPA implement, at a minimum, via label modifications and county bulletins, the applicable Reasonable and Prudent Alternative measure identified in 1989 Biological Opinions. EPA should also implement the risk reduction and mitigative measures identified in the OP ecological risk assessment documents to reduce hazards to non-target organisms.

Response: EPA is in the process of developing county-specific bulletins that specify measures to protect endangered and threatened species. Although bulletins have not yet been developed for all counties where they will be needed, EPA has included the pesticide use provisions from the 1989 Biological Opinion (as well as other opinions) or equivalent protective measures in the over 300 bulletins that have been completed and distributed.

The mitigation measures suggested in the Preliminary Environmental Fate and Ecological Risk assessments, along with other measures that may be put forward during the comment period, will be considered in developing risk management options for these seven OPs. As noted previously, the opportunity for the public to provide comment on risk management options will also be subject to a 60-day period.